

In Vitro Safety "Clinical Trial" of the Cardiac Liability of Hydroxychloroquine and Azithromycin as COVID19 Polytherapy.

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Public Summary:

Scientific Abstract:

Despite global efforts, there are no effective FDA-approved medicines for the treatment of SARS-CoV-2 infection. Potential therapeutics focus on repurposed drugs, some with cardiac liabilities. Here we report on a preclinical drug screening platform, a cardiac microphysiological system (MPS), to assess cardiotoxicity associated with hydroxychloroquine (HCQ) and azithromycin (AZM) polytherapy in a mock clinical trial. The MPS contained human heart muscle derived from patient-specific induced pluripotent stem cells. The effect of drug response was measured using outputs that correlate with clinical measurements such as QT interval (action potential duration) and drug-biomarker pairing. Chronic exposure to HCQ alone elicited early afterdepolarizations (EADs) and increased QT interval from day 6 onwards. AZM alone elicited an increase in QT interval from day 7 onwards and arrhythmias were observed at days 8 and 10. Monotherapy results closely mimicked clinical trial outcomes. Upon chronic exposure to HCQ and AZM polytherapy, we observed an increase in QT interval on days 4-8.. Interestingly, a decrease in arrhythmias and instabilities was observed in polytherapy relative to monotherapy, in concordance with published clinical trials. Furthermore, biomarkers, most of them measurable in patients' serum, were identified for negative effects of single drug or polytherapy on tissue contractile function, morphology, and antioxidant protection. The cardiac MPS can predict clinical arrhythmias associated with QT prolongation and rhythm instabilities. This high content system can help clinicians design their trials, rapidly project cardiac outcomes, and define new monitoring biomarkers to accelerate access of patients to safe COVID-19 therapeutics.

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